internucleotide linkages within the wing portions of the chimeric structures and sulfurization utilizing 3,H-1,2 benzodithiole-3-one 1,1 dioxide (Beaucage Reagent) to generate the phosphorothioate internucleotide linkages for the center gap.

Other chimeric oligonucleotides, chimeric oligonucleosides and mixed chimeric oligonucleotides/oligonucleosides are synthesized according to United States patent 5,623,065, herein incorporated by reference.

Example 6

Oligonucleotide Isolation

After cleavage from the controlled pore glass column (Applied Biosystems) and deblocking in concentrated ammonium hydroxide at 55°C for 18 hours, the oligonucleotides or oligonucleosides are purified by precipitation twice out of 0.5 M NaCl with 2.5 volumes ethanol. Synthesized oligonucleotides were analyzed by polyacrylamide gel electrophoresis on denaturing gels and judged to be at least 85% full length material. The relative amounts of phosphorothioate and phosphodiester linkages obtained in synthesis were periodically checked by ^{31}P nuclear magnetic resonance spectroscopy, and for some studies oligonucleotides were purified by HPLC, as described by Chiang et al., *J. Biol. Chem.* **1991**, *266*, 18162-18171. Results obtained with HPLC-purified material were similar to those obtained with non-HPLC purified material.

Example 7

Oligonucleotide Synthesis - 96 Well Plate Format

Oligonucleotides were synthesized via solid phase P(III) phosphoramidite chemistry on an automated synthesizer capable of assembling 96 sequences simultaneously in a standard 96 well format. Phosphodiester internucleotide linkages were afforded by oxidation with aqueous iodine. Phosphorothioate internucleotide linkages were generated by sulfurization utilizing 3,H-1,2 benzodithiole-3-one 1,1 dioxide (Beaucage Reagent) in anhydrous acetonitrile. Standard base-protected beta-cyanoethyldiisopropyl phosphoramidites were purchased from

commercial vendors (e.g. PE-Applied Biosystems, Foster City, CA, or Pharmacia, Piscataway, NJ). Non-standard nucleosides are synthesized as per known literature or patented methods. They are utilized as base protected beta-cyanoethyldiisopropyl phosphoramidites.

Oligonucleotides were cleaved from support and deprotected with concentrated NH_4OH at elevated temperature (55-60°C) for 12-16 hours and the released product then dried in vacuo. The dried product was then re-suspended in sterile water to afford a master plate from which all analytical and test plate samples are then diluted utilizing robotic pipettors.

Example 8

Oligonucleotide Analysis - 96 Well Plate Format

The concentration of oligonucleotide in each well was assessed by dilution of samples and UV absorption spectroscopy. The full-length integrity of the individual products was evaluated by capillary electrophoresis (CE) in either the 96 well format (Beckman P/ACE™ MDQ) or, for individually prepared samples, on a commercial CE apparatus (e.g., Beckman P/ACE™ 5000, ABI 270). Base and backbone composition was confirmed by mass analysis of the compounds utilizing electrospray-mass spectroscopy. All assay test plates were diluted from the master plate using single and multi-channel robotic pipettors. Plates were judged to be acceptable if at least 85% of the compounds on the plate were at least 85% full length.

Example 9

Cell culture and oligonucleotide treatment

The effect of antisense compounds on target nucleic acid expression can be tested in any of a variety of cell types provided that the target nucleic acid is present at measurable levels. This can be routinely determined using, for example, PCR or Northern blot analysis. The following 5 cell types are provided for illustrative purposes, but other cell types can be routinely used, provided that the target is expressed in the cell type chosen. This can be readily determined by methods routine in the art, for example Northern blot analysis,

Ribonuclease protection assays, or RT-PCR.

T-24 cells:

The human transitional cell bladder carcinoma cell line T-24 was obtained from the American Type Culture Collection (ATCC) (Manassas, VA). T-24 cells were routinely cultured in complete McCoy's 5A basal media (Invitrogen Corporation, Carlsbad, CA) supplemented with 10% fetal calf serum ((Invitrogen Corporation, Carlsbad, CA), penicillin 100 units per mL, and streptomycin 100 micrograms per mL (Invitrogen Corporation, Carlsbad, CA). Cells were routinely passaged by trypsinization and dilution when they reached 90% confluence. Cells were seeded into 96-well plates (Falcon-Primaria #3872) at a density of 7000 cells/well for use in RT-PCR analysis.

For Northern blotting or other analysis, cells may be seeded onto 100 mm or other standard tissue culture plates and treated similarly, using appropriate volumes of medium and oligonucleotide.

A549 cells:

The human lung carcinoma cell line A549 was obtained from the American Type Culture Collection (ATCC) (Manassas, VA). A549 cells were routinely cultured in DMEM basal media (Invitrogen Corporation, Carlsbad, CA) supplemented with 10% fetal calf serum (Invitrogen Corporation, Carlsbad, CA), penicillin 100 units per mL, and streptomycin 100 micrograms per mL (Invitrogen Corporation, Carlsbad, CA). Cells were routinely passaged by trypsinization and dilution when they reached 90% confluence.

NHDF cells:

Human neonatal dermal fibroblast (NHDF) were obtained from the Clonetics Corporation (Walkersville, MD). NHDFs were routinely maintained in Fibroblast Growth Medium (Clonetics Corporation, Walkersville, MD) supplemented as recommended by the supplier. Cells were maintained for up to 10 passages as recommended by the supplier.

HEK cells:

Human embryonic keratinocytes (HEK) were obtained from the Clonetics Corporation (Walkersville, MD). HEKs were routinely maintained in Keratinocyte Growth Medium (Clonetics Corporation, Walkersville, MD) formulated as recommended by the supplier. Cells were routinely maintained for up to 10 passages as recommended by the supplier.

MCF7:

The human breast carcinoma cell line MCF-7 was obtained from the American Type Culture Collection (Manassas, VA). MCF-7 cells were routinely cultured in DMEM low glucose (Gibco/Life Technologies, Gaithersburg, MD) supplemented with 10% fetal calf serum (Gibco/Life Technologies, Gaithersburg, MD). Cells were routinely passaged by trypsinization and dilution when they reached 90% confluence. Cells were seeded into 96-well plates (Falcon-Primaria #3872) at a density of 7000 cells/well for use in RT-PCR analysis.

For Northern blotting or other analyses, cells may be seeded onto 100 mm or other standard tissue culture plates and treated similarly, using appropriate volumes of medium and oligonucleotide.

Treatment with antisense compounds:

When cells reached 70% confluency, they were treated with oligonucleotide. For cells grown in 96-well plates, wells were washed once with 100 µL OPTI-MEM™-1 reduced-serum medium (Invitrogen Corporation, Carlsbad, CA) and then treated with 130 µL of OPTI-MEM™-1 containing 3.75 µg/mL LIPOFECTIN™ (Invitrogen Corporation, Carlsbad, CA) and the desired concentration of oligonucleotide. After 4-7 hours of treatment, the medium was replaced with fresh medium. Cells were harvested 16-24 hours after oligonucleotide treatment.

The concentration of oligonucleotide used varies from cell line to cell line. To determine the optimal oligonucleotide concentration for a particular cell line, the cells are treated with a positive control oligonucleotide at a range of concentrations. For human cells the positive control

oligonucleotide is ISIS 13920, **TCC**GTCATCGCT**CCTCAGGG**, SEQ ID NO: 1, a 2'-O-methoxyethyl gapmer (2'-O-methoxyethyls shown in bold) with a phosphorothioate backbone which is targeted to human H-ras. For mouse or rat cells the positive control oligonucleotide is ISIS 15770, **ATGCA**TTCTGCCCCC**AAGGA**, SEQ ID NO: 2, a 2'-O-methoxyethyl gapmer (2'-O-methoxyethyls shown in bold) with a phosphorothioate backbone which is targeted to both mouse and rat c-raf. The concentration of positive control oligonucleotide that results in 80% inhibition of c-Ha-ras (for ISIS 13920) or c-raf (for ISIS 15770) mRNA is then utilized as the screening concentration for new oligonucleotides in subsequent experiments for that cell line. If 80% inhibition is not achieved, the lowest concentration of positive control oligonucleotide that results in 60% inhibition of H-ras or c-raf mRNA is then utilized as the oligonucleotide screening concentration in subsequent experiments for that cell line. If 60% inhibition is not achieved, that particular cell line is deemed as unsuitable for oligonucleotide transfection experiments.

Example 10

Analysis of oligonucleotide inhibition of mucin 1, transmembrane expression

Antisense modulation of mucin 1, transmembrane expression can be assayed in a variety of ways known in the art. For example, mucin 1, transmembrane mRNA levels can be quantitated by, e.g., Northern blot analysis, competitive polymerase chain reaction (PCR), or real-time PCR (RT-PCR). Real-time quantitative PCR is presently preferred. RNA analysis can be performed on total cellular RNA or poly(A)+ mRNA. The preferred method of RNA analysis of the present invention is the use of total cellular RNA as described in other examples herein. Methods of RNA isolation are taught in, for example, Ausubel, F.M. *et al.*, *Current Protocols in Molecular Biology*, Volume 1, pp. 4.1.1-4.2.9 and 4.5.1-4.5.3, John Wiley & Sons, Inc., **1993**. Northern blot analysis is routine in the art and is taught in, for example, Ausubel, F.M. et al., *Current Protocols in Molecular Biology*, Volume 1, pp. 4.2.1-4.2.9, John Wiley & Sons,

Inc., **1996**. Real-time quantitative (PCR) can be conveniently accomplished using the commercially available ABI PRISM™ 7700 Sequence Detection System, available from PE-Applied Biosystems, Foster City, CA and used according to manufacturer's instructions.

Protein levels of mucin 1, transmembrane can be quantitated in a variety of ways well known in the art, such as immunoprecipitation, Western blot analysis (immunoblotting), ELISA or fluorescence-activated cell sorting (FACS). Antibodies directed to mucin 1, transmembrane can be identified and obtained from a variety of sources, such as the MSRS catalog of antibodies (Aerie Corporation, Birmingham, MI), or can be prepared via conventional antibody generation methods. Methods for preparation of polyclonal antisera are taught in, for example, Ausubel, F.M. et al., *Current Protocols in Molecular Biology*, Volume 2, pp. 11.12.1-11.12.9, John Wiley & Sons, Inc., **1997**. Preparation of monoclonal antibodies is taught in, for example, Ausubel, F.M. et al., *Current Protocols in Molecular Biology*, Volume 2, pp. 11.4.1-11.11.5, John Wiley & Sons, Inc., **1997**.

Immunoprecipitation methods are standard in the art and can be found at, for example, Ausubel, F.M. et al., *Current Protocols in Molecular Biology*, Volume 2, pp. 10.16.1-10.16.11, John Wiley & Sons, Inc., **1998**. Western blot (immunoblot) analysis is standard in the art and can be found at, for example, Ausubel, F.M. et al., *Current Protocols in Molecular Biology*, Volume 2, pp. 10.8.1-10.8.21, John Wiley & Sons, Inc., **1997**. Enzyme-linked immunosorbent assays (ELISA) are standard in the art and can be found at, for example, Ausubel, F.M. et al., *Current Protocols in Molecular Biology*, Volume 2, pp. 11.2.1-11.2.22, John Wiley & Sons, Inc., **1991**.

Example 11

Poly(A)+ mRNA isolation

Poly(A)+ mRNA was isolated according to Miura et al., *Clin. Chem.*, **1996**, *42*, 1758-1764. Other methods for poly(A)+ mRNA isolation are taught in, for example, Ausubel, F.M. et al., *Current Protocols in Molecular Biology*, Volume 1, pp. 4.5.1-

4.5.3, John Wiley & Sons, Inc., **1993**. Briefly, for cells grown on 96-well plates, growth medium was removed from the cells and each well was washed with 200 µL cold PBS. 60 µL lysis buffer (10 mM Tris-HCl, pH 7.6, 1 mM EDTA, 0.5 M NaCl, 0.5% NP-40, 20 mM vanadyl-ribonucleoside complex) was added to each well, the plate was gently agitated and then incubated at room temperature for five minutes. 55 µL of lysate was transferred to Oligo d(T) coated 96-well plates (AGCT Inc., Irvine CA). Plates were incubated for 60 minutes at room temperature, washed 3 times with 200 µL of wash buffer (10 mM Tris-HCl pH 7.6, 1 mM EDTA, 0.3 M NaCl). After the final wash, the plate was blotted on paper towels to remove excess wash buffer and then air-dried for 5 minutes. 60 µL of elution buffer (5 mM Tris-HCl pH 7.6), preheated to 70°C was added to each well, the plate was incubated on a 90°C hot plate for 5 minutes, and the eluate was then transferred to a fresh 96-well plate.

Cells grown on 100 mm or other standard plates may be treated similarly, using appropriate volumes of all solutions.

Example 12

Total RNA Isolation

Total RNA was isolated using an RNEASY 96™ kit and buffers purchased from Qiagen Inc. (Valencia, CA) following the manufacturer's recommended procedures. Briefly, for cells grown on 96-well plates, growth medium was removed from the cells and each well was washed with 200 µL cold PBS. 150 µL Buffer RLT was added to each well and the plate vigorously agitated for 20 seconds. 150 µL of 70% ethanol was then added to each well and the contents mixed by pipetting three times up and down. The samples were then transferred to the RNEASY 96™ well plate attached to a QIAVAC™ manifold fitted with a waste collection tray and attached to a vacuum source. Vacuum was applied for 1 minute. 500 µL of Buffer RW1 was added to each well of the RNEASY 96™ plate and incubated for 15 minutes and the vacuum was again applied for 1 minute. An additional 500 µL of Buffer RW1

was added to each well of the RNEASY 96™ plate and the vacuum was applied for 2 minutes. 1 mL of Buffer RPE was then added to each well of the RNEASY 96™ plate and the vacuum applied for a period of 90 seconds. The Buffer RPE wash was then repeated and the vacuum was applied for an additional 3 minutes. The plate was then removed from the QIAVAC™ manifold and blotted dry on paper towels. The plate was then re-attached to the QIAVAC™ manifold fitted with a collection tube rack containing 1.2 mL collection tubes. RNA was then eluted by pipetting 170 µL water into each well, incubating 1 minute, and then applying the vacuum for 3 minutes.

The repetitive pipetting and elution steps may be automated using a QIAGEN Bio-Robot 9604 (Qiagen, Inc., Valencia CA). Essentially, after lysing of the cells on the culture plate, the plate is transferred to the robot deck where the pipetting, DNase treatment and elution steps are carried out.

Example 13

Real-time Quantitative PCR Analysis of mucin 1, transmembrane mRNA Levels

Quantitation of mucin 1, transmembrane mRNA levels was determined by real-time quantitative PCR using the ABI PRISM™ 7700 Sequence Detection System (PE-Applied Biosystems, Foster City, CA) according to manufacturer's instructions. This is a closed-tube, non-gel-based, fluorescence detection system which allows high-throughput quantitation of polymerase chain reaction (PCR) products in real-time. As opposed to standard PCR, in which amplification products are quantitated after the PCR is completed, products in real-time quantitative PCR are quantitated as they accumulate. This is accomplished by including in the PCR reaction an oligonucleotide probe that anneals specifically between the forward and reverse PCR primers, and contains two fluorescent dyes. A reporter dye (e.g., FAM, obtained from either Operon Technologies Inc., Alameda, CA or Integrated DNA Technologies Inc., Coralville, IA) is attached to the 5' end of the probe and a quencher dye (e.g.,

TAMRA, obtained from either Operon Technologies Inc., Alameda, CA or Integrated DNA Technologies Inc., Coralville, IA) is attached to the 3' end of the probe. When the probe and dyes are intact, reporter dye emission is quenched by the proximity of the 3' quencher dye. During amplification, annealing of the probe to the target sequence creates a substrate that can be cleaved by the 5'-exonuclease activity of Taq polymerase. During the extension phase of the PCR amplification cycle, cleavage of the probe by Taq polymerase releases the reporter dye from the remainder of the probe (and hence from the quencher moiety) and a sequence-specific fluorescent signal is generated. With each cycle, additional reporter dye molecules are cleaved from their respective probes, and the fluorescence intensity is monitored at regular intervals by laser optics built into the ABI PRISM™ 7700 Sequence Detection System. In each assay, a series of parallel reactions containing serial dilutions of mRNA from untreated control samples generates a standard curve that is used to quantitate the percent inhibition after antisense oligonucleotide treatment of test samples.

Prior to quantitative PCR analysis, primer-probe sets specific to the target gene being measured are evaluated for their ability to be "multiplexed" with a GAPDH amplification reaction. In multiplexing, both the target gene and the internal standard gene GAPDH are amplified concurrently in a single sample. In this analysis, mRNA isolated from untreated cells is serially diluted. Each dilution is amplified in the presence of primer-probe sets specific for GAPDH only, target gene only ("single-plexing"), or both (multiplexing). Following PCR amplification, standard curves of GAPDH and target mRNA signal as a function of dilution are generated from both the single-plexed and multiplexed samples. If both the slope and correlation coefficient of the GAPDH and target signals generated from the multiplexed samples fall within 10% of their corresponding values generated from the single-plexed samples, the primer-probe set specific for that target is deemed multiplexable. Other methods of PCR are also known in the art.

PCR reagents were obtained from Invitrogen, Carlsbad, CA. RT-PCR reactions were carried out by adding 20 μL PCR cocktail

(2.5x PCR buffer (-MgCl2), 6.6 mM MgCl2, 375 μM each of dATP, dCTP, dCTP and dGTP, 375 nM each of forward primer and reverse primer, 125 nM of probe, 4 Units RNAse inhibitor, 1.25 Units PLATINUM® Taq, 5 Units MuLV reverse transcriptase, and 2.5x ROX dye) to 96 well plates containing 30 μL total RNA solution. The RT reaction was carried out by incubation for 30 minutes at 48°C. Following a 10 minute incubation at 95°C to activate the PLATINUM® Taq, 40 cycles of a two-step PCR protocol were carried out: 95°C for 15 seconds (denaturation) followed by 60°C for 1.5 minutes (annealing/extension).

Gene target quantities obtained by real time RT-PCR are normalized using either the expression level of GAPDH, a gene whose expression is constant, or by quantifying total RNA using RiboGreenTM (Molecular Probes, Inc. Eugene, OR). GAPDH expression is quantified by real time RT-PCR, by being run simultaneously with the target, multiplexing, or separately. Total RNA is quantified using RiboGreenTM RNA quantification reagent from Molecular Probes. Methods of RNA quantification by RiboGreenTM are taught in Jones, L.J., et al, Analytical Biochemistry, 1998, 265, 368-374.

In this assay, 170 μL of RiboGreenTM working reagent (RiboGreenTM reagent diluted 1:350 in 10mM Tris-HCl, 1 mM EDTA, pH 7.5) is pipetted into a 96-well plate containing 30 μL purified, cellular RNA. The plate is read in a CytoFluor 4000 (PE Applied Biosystems) with excitation at 480nm and emission at 520nm.

Probes and primers to human mucin 1, transmembrane were designed to hybridize to a human mucin 1, transmembrane sequence, using published sequence information (GenBank accession number NM_002456.1, incorporated herein as SEQ ID NO:3). For human mucin 1, transmembrane the PCR primers were: forward primer: TGACTCTGGCCTTCCGAGAA (SEQ ID NO: 4) reverse primer: GCTGCTTCCGTTTTATACTGATTG (SEQ ID NO: 5) and the PCR probe was: FAM-TACCATCAATGTCCACGACGTGGAGACA-TAMRA (SEQ ID NO: 6) where FAM (PE-Applied Biosystems, Foster City, CA) is the fluorescent reporter dye) and TAMRA (PE-Applied Biosystems, Foster City, CA) is the quencher dye. For human

GAPDH the PCR primers were:
forward primer: GAAGGTGAAGGTCGGAGTC(SEQ ID NO:7)
reverse primer: GAAGATGGTGATGGGATTTC (SEQ ID NO:8) and the PCR probe was: 5' JOE-CAAGCTTCCCGTTCTCAGCC-TAMRA 3' (SEQ ID NO: 9) where JOE (PE-Applied Biosystems, Foster City, CA) is the fluorescent reporter dye) and TAMRA (PE-Applied Biosystems, Foster City, CA) is the quencher dye.

Example 14

Northern blot analysis of mucin 1, transmembrane mRNA levels

Eighteen hours after antisense treatment, cell monolayers were washed twice with cold PBS and lysed in 1 mL RNAZOL™ (TEL-TEST "B" Inc., Friendswood, TX). Total RNA was prepared following manufacturer's recommended protocols. Twenty micrograms of total RNA was fractionated by electrophoresis through 1.2% agarose gels containing 1.1% formaldehyde using a MOPS buffer system (AMRESCO, Inc. Solon, OH). RNA was transferred from the gel to HYBOND™-N+ nylon membranes (Amersham Pharmacia Biotech, Piscataway, NJ) by overnight capillary transfer using a Northern/Southern Transfer buffer system (TEL-TEST "B" Inc., Friendswood, TX). RNA transfer was confirmed by UV visualization. Membranes were fixed by UV cross-linking using a STRATALINKER™ UV Crosslinker 2400 (Stratagene, Inc, La Jolla, CA) and then probed using QUICKHYB™ hybridization solution (Stratagene, La Jolla, CA) using manufacturer's recommendations for stringent conditions.

To detect human mucin 1, transmembrane, a human mucin 1, transmembrane specific probe was prepared by PCR using the forward primer TGACTCTGGCCTTCCGAGAA (SEQ ID NO: 4) and the reverse primer GCTGCTTCCGTTTTATACTGATTG (SEQ ID NO: 5). To normalize for variations in loading and transfer efficiency membranes were stripped and probed for human glyceraldehyde-3-phosphate dehydrogenase (GAPDH) RNA (Clontech, Palo Alto, CA).

Hybridized membranes were visualized and quantitated using a PHOSPHORIMAGER™ and IMAGEQUANT™ Software V3.3 (Molecular Dynamics, Sunnyvale, CA). Data was normalized to GAPDH levels

in untreated controls.

Example 15

Antisense inhibition of human mucin 1, transmembrane expression by chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a deoxy gap

In accordance with the present invention, a series of oligonucleotides were designed to target different regions of the human mucin 1, transmembrane RNA, using published sequences (GenBank accession number NM_002456.1, representing the main mRNA of mucin 1, transmembrane, incorporated herein as SEQ ID NO: 3; GenBank accession number AF125525.1, representing the variant MUC1/Y, incorporated herein as SEQ ID NO: 10; GenBank accession number AF348143.1, representing a variant of mucin 1, transmembrane herein designated MUC1-II, incorporated herein as SEQ ID NO: 11; GenBank accession number AI834269.1, representing a variant of mucin 1, transmembrane herein designated MUC1-III, the complement of which is incorporated herein as SEQ ID NO: 12; GenBank accession number AW369441.1, representing a variant of mucin 1, transmembrane herein designated MUC1-IV, incorporated herein as SEQ ID NO: 14; GenBank accession number BG774910.1, representing a variant of mucin 1, transmembrane herein designated MUC1-V, incorporated herein as SEQ ID NO: 16; GenBank accession number J05581.1, representing a variant of mucin 1, transmembrane herein designated MUC1-VI, incorporated herein as SEQ ID NO: 17; GenBank accession number M31823.1, representing a variant of mucin 1, transmembrane herein designated MUC1-VII, incorporated herein as SEQ ID NO: 18; GenBank accession number M61170, representing a genomic sequence of mucin 1, transmembrane, incorporated herein as SEQ ID NO: 19; GenBank accession number U60259.1, representing the variant MUC1/X, incorporated herein as SEQ ID NO: 20; and GenBank accession number Z17325.1, representing the variant MUC1/D, incorporated herein as SEQ ID NO: 21). The oligonucleotides are shown in Table 1. "Target site" indicates the first (5'-most) nucleotide number on the particular target sequence to which the oligonucleotide binds. All compounds in Table 1 are chimeric

oligonucleotides ("gapmers") 20 nucleotides in length, composed of a central "gap" region consisting of ten 2'-deoxynucleotides, which is flanked on both sides (5' and 3' directions) by five-nucleotide "wings". The wings are composed of 2'-methoxyethyl (2'-MOE)nucleotides. The internucleoside (backbone) linkages are phosphorothioate (P=S) throughout the oligonucleotide. All cytidine residues are 5-methylcytidines. The compounds were analyzed for their effect on human mucin 1, transmembrane mRNA levels by quantitative real-time PCR as described in other examples herein. Data are averages from two experiments. If present, "N.D." indicates "no data".

Table 1

Inhibition of human mucin 1, transmembrane mRNA levels by chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a deoxy gap

ISIS #	REGION	TARGET SEQ ID NO	TARGET SITE	SEQUENCE	% INHIB	SEQ ID NO
199396	5'UTR	3	8	gaacagattcaagcagccag	0	22
199397	Start Codon	3	49	cccggtgtcatggtggtggt	58	23
199398	Start Codon	3	52	gtgcccggtgtcatggtggt	58	24
199399	Coding	3	65	gaaaggagactgggtgcccg	54	25
199400	Coding	3	105	ctgtaacaactgtaagcact	41	26
199401	Coding	3	107	acctgtaacaactgtaagca	53	27
199402	Coding	3	187	tcagtagagctgggcactga	55	28
199403	Coding	3	196	gcattcttctcagtagagct	77	29
199404	Coding	3	197	agcattcttctcagtagagc	50	30
199405	Coding	3	210	tggtcatactcacagcattc	42	31
199406	Coding	3	214	ctgctggtcatactcacagc	56	32
199407	Coding	3	227	gctggagagtacgctgctgg	57	33
199408	Coding	3	344	tgggaccgaggtgacatcct	65	34
199409	Coding	3	694	gtgacattgtggactggagg	55	35
199410	Coding	3	697	gaggtgacattgtggactgg	57	36
199411	Coding	3	704	tgaggccgaggtgacattgt	54	37
199412	Coding	3	829	gtggtaggagtatcagagtg	53	38
199413	Coding	3	835	gcaagggtggtaggagtatc	50	39
199414	Coding	3	860	ggcatcagtcttggtgctat	53	40
199415	Coding	3	940	gagaccccagtagacaactg	24	41
199416	Coding	3	997	tcttccagagaggaattaaa	41	42
199417	Coding	3	1037	aatgtctctctgcagctctt	41	43
199418	Coding	3	1042	tcagaaatgtctctctgcag	54	44
199419	Coding	3	1056	tctgcaaaaacatttcagaa	45	45

199420	Coding	3	1065	gtttataaatctgcaaaaac	39	46
199421	Coding	3	1091	attggagaggcccagaaaac	41	47
199422	Coding	3	1095	taatattggagaggcccaga	50	48
199423	Coding	3	1100	gaacttaatattggagaggc	48	49
199424	Coding	3	1112	agatcctggcctgaacttaa	53	50
199425	Coding	3	1115	cacagatcctggcctgaact	49	51
199426	Coding	3	1168	acgtcgtggacattgatggt	84	52
199427	Coding	3	1217	gttatatcgagaggctgctt	50	53
199428	Coding	3	1225	atcgtcaggttatatcgaga	47	54
199429	Coding	3	1251	gcacatcactcacgctgacg	50	55
199430	Coding	3	1268	ggcagagaaaggaaatggca	46	56
199431	Coding	3	1371	gacagacagccaaggcaatg	47	57
199432	Coding	3	1397	ctgcccgtagttctttcggc	43	58
199433	Coding	3	1412	tggaaagatgtccagctgcc	41	59
199434	Coding	3	1499	gctacgatcggtactgctag	52	60
199435	Coding	3	1540	aggctgctgccaccattacc	59	61
199436	Coding	3	1582	aagttggcagaagtggctgc	42	62
199437	Stop Codon	3	1586	ctacaagttggcagaagtgg	35	63
199438	Stop Codon	3	1594	acgtgcccctacaagttggc	57	64
199439	3'UTR	3	1606	gctcagagggcgacgtgccc	36	65
199440	3'UTR	3	1617	ctggccactcagctcagagg	56	66
199441	3'UTR	3	1622	actggctggccactcagctc	55	67
199442	3'UTR	3	1630	ggaatggcactggctggcca	60	68
199443	3'UTR	3	1635	ggagtggaatggcactggct	56	69
199444	Coding	10	141	aggaattaaaagcattcttc	7	70
199445	Coding	11	174	cagtagacaaagcattcttc	40	71
199446	Coding	11	297	gacagacagccatttcagaa	80	72
199447	Exon: Exon Junction	12	49	catcactcactgaacttaat	1	73
199448	Intron 6	19	5327	tttgggttttccaagtaccc	83	74
199449	Intron 6	19	5436	catagtctcctcccaggcct	44	75
199450	Intron 6	19	5588	cattttgcctctgggtgcaa	49	76
199451	Exon: Exon Junction	14	160	cagccccagacatttcagaa	21	77
199452	Intron 1	19	3289	ttctctctgcccataggcct	42	78
199453	Intron 1	19	3426	gggtctttatgaaggaaaaa	43	79
199454	Exon: Exon Junction	16	455	acatcactcacatttcagaa	62	80
199455	3'UTR	17	1776	accacgttttattcagtcca	65	81
199456	Coding	18	115	gctgtggtagctgtaagcac	38	82
199457	Coding	20	175	gtgctgggatagcattcttc	15	83
199458	Coding	20	245	agagtcaattgtaccaccac	2	84
199459	Coding	21	122	ttttctccacctgtaagcac	18	85
199460	Intron: Exon Junction	19	3489	cctgtaacaactgttgcggg	32	86
199461	Intron: Exon	19	3498	tgaccagaacctgtaacaac	38	87

	Junction					
199462	Exon 2d	19	3530	tctccttttctccacctggg	49	88
199463	Exon 2d	19	3571	ctcagtagagctgggcactg	47	89
199464	Exon 2d	19	3590	tcatactcacagcattcttc	42	90
199465	Exon: Intron Junction	19	3973	agagcctgaggccgaggtga	58	91
199466	Intron: Exon Junction	19	4201	gaccccagtagacaactggg	20	92
199467	Intron: Exon Junction	19	4250	aggaattaaactggaggttt	55	93
199468	Exon 3d	19	4269	gtgctgggatcttccagaga	61	94
199469	Intron: Exon Junction	19	4621	atcctggcctggtcacaggg	39	95
199470	Exon 5	19	4936	cagccccagactgggcagag	41	96
199471	Intron 6	19	5449	ggccccttttcttccatagtc	55	97
199472	Intron 6	19	5889	ccacctggagtggttttcca	42	98
199473	Intron 6	19	5956	aaagccgagagagggaggtc	51	99

As shown in Table 1, SEQ ID NOs 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 42, 43, 44, 45, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 64, 66, 67, 68, 69, 72, 74, 75, 76, 78, 79, 80, 81, 88, 89, 90, 91, 93, 94, 96, 97, 98 and 99 demonstrated at least 41% inhibition of human mucin 1, transmembrane expression in this assay and are therefore preferred. The target sites to which these preferred sequences are complementary are herein referred to as "active sites" and are therefore preferred sites for targeting by compounds of the present invention.

Example 16

Western blot analysis of mucin 1, transmembrane protein levels

Western blot analysis (immunoblot analysis) is carried out using standard methods. Cells are harvested 16-20 h after oligonucleotide treatment, washed once with PBS, suspended in Laemmli buffer (100 ul/well), boiled for 5 minutes and loaded on a 16% SDS-PAGE gel. Gels are run for 1.5 hours at 150 V, and transferred to membrane for western blotting. Appropriate primary antibody directed to mucin 1, transmembrane is used,

with a radiolabelled or fluorescently labeled secondary antibody directed against the primary antibody species. Bands are visualized using a PHOSPHORIMAGER™ (Molecular Dynamics, Sunnyvale CA).

Example 17

Targeting of individual oligonucleotides to specific variants of mucin 1, transmembrane

It is advantageous to selectively inhibit the expression of one or more variants of mucin 1, transmembrane. Consequently, in one embodiment of the present invention are oligonucleotides that selectively target, hybridize to, and specifically inhibit one or more, but fewer than all of the variants of mucin 1, transmembrane. A summary of the target sites of the variants is shown in Table 2 and includes Genbank accession number NM_002456.1, representing mucin 1, transmembrane (MUC1), incorporated herein as SEQ ID NO: 3; Genbank accession number AF125525.1, representing MUC1/Y, incorporated herein as SEQ ID NO: 10; Genbank accession number AF348143.1, representing MUC1-II, incorporated herein as SEQ ID NO: 11; Genbank accession number AI834269.1, representing MUC1-III, incorporated herein as SEQ ID NO: 12; Genbank accession number AW369441.1, representing MUC1-IV, incorporated herein as SEQ ID NO: 14; Genbank accession number BG774910.1, representing MUC1-V, incorporated herein as SEQ ID NO: 16; Genbank accession number J05581.1, representing MUC1-VI, incorporated herein as SEQ ID NO: 17; Genbank accession number M31823.1, representing MUC1-VII, incorporated herein as SEQ ID NO: 18; Genbank accession number U60259.1, representing MUC1/X, incorporated herein as SEQ ID NO: 20; Genbank accession number Z17325.1, representing MUC1/D, incorporated herein as SEQ ID NO: 21; Genbank accession number S81781.1, representing the variant MUC1/A, incorporated herein as SEQ ID NO: 100; Genbank accession number M32738.1, representing the variant MUC1/REP, incorporated herein as SEQ ID NO: 101; Genbank accession number M35093.1, representing the variant MUC1/SEC, incorporated herein as SEQ ID NO: 102; Genbank accession number U60261.1, representing the variant MUC1/Z, incorporated herein as SEQ ID NO: 103; Genbank accession number Z17324.1, representing the

variant MUC1/C, incorporated herein as SEQ ID NO: 104; Genbank accession number BF876382.1, representing a variant of mucin 1, transmembrane herein designated MUC1-VIII, incorporated herein as SEQ ID NO: 105; Genbank accession number BG541121.1, representing a variant of mucin 1, transmembrane herein designated MUC1-IX, incorporated herein as SEQ ID NO: 106; Genbank accession number AL046435.1, representing a variant of mucin 1, transmembrane herein designated MUC1-X, incorporated herein as SEQ ID NO: 107.

Table 2

Targeting of individual oligonucleotides to specific variants of mucin 1, transmembrane

ISIS #	OLIGO SEQ ID NO.	TARGET SITE	VARIANT	VARIANT SEQ ID NO.
199396	22	8	MUC1	3
199397	23	49	MUC1	3
199397	23	16	MUC1-II	11
199397	23	64	MUC1-VI	17
199397	23	58	MUC1-VII	18
199397	23	17	MUC1/X	20
199397	23	65	MUC1/D	21
199397	23	1	MUC1/A	100
199397	23	42	MUC1/REP	101
199397	23	776	MUC1/SEC	102
199397	23	17	MUC1/Z	103
199397	23	65	MUC1/C	104
199397	23	59	MUC1-IX	106
199398	24	52	MUC1	3
199398	24	19	MUC1-II	11
199398	24	67	MUC1-VI	17
199398	24	61	MUC1-VII	18
199398	24	20	MUC1/X	20
199398	24	68	MUC1/D	21
199398	24	4	MUC1/A	100
199398	24	45	MUC1/REP	101
199398	24	779	MUC1/SEC	102
199398	24	20	MUC1/Z	103
199398	24	68	MUC1/C	104
199398	24	62	MUC1-IX	106
199399	25	65	MUC1	3
199399	25	8	MUC1/Y	10
199399	25	32	MUC1-II	11
199399	25	80	MUC1-VI	17
199399	25	74	MUC1-VII	18
199399	25	33	MUC1/X	20

199399	25	81	MUC1/D	21
199399	25	17	MUC1/A	100
199399	25	58	MUC1/REP	101
199399	25	792	MUC1/SEC	102
199399	25	33	MUC1/Z	103
199399	25	81	MUC1/C	104
199399	25	75	MUC1-IX	106
199400	26	105	MUC1	3
199400	26	72	MUC1-II	11
199400	26	120	MUC1-VI	17
199400	26	73	MUC1/X	20
199400	26	73	MUC1/Z	103
199401	27	107	MUC1	3
199401	27	74	MUC1-II	11
199401	27	122	MUC1-VI	17
199401	27	75	MUC1/X	20
199401	27	75	MUC1/Z	103
199402	28	187	MUC1	3
199402	28	121	MUC1/Y	10
199402	28	154	MUC1-II	11
199402	28	202	MUC1-VI	17
199402	28	223	MUC1-VII	18
199402	28	155	MUC1/X	20
199402	28	166	MUC1/A	100
199402	28	207	MUC1/REP	101
199402	28	1413	MUC1/SEC	102
199402	28	155	MUC1/Z	103
199402	28	346	MUC1-VIII	105
199402	28	224	MUC1-IX	106
199403	29	196	MUC1	3
199403	29	130	MUC1/Y	10
199403	29	163	MUC1-II	11
199403	29	211	MUC1-VI	17
199403	29	232	MUC1-VII	18
199403	29	164	MUC1/X	20
199403	29	175	MUC1/A	100
199403	29	216	MUC1/REP	101
199403	29	1422	MUC1/SEC	102
199403	29	164	MUC1/Z	103
199403	29	355	MUC1-VIII	105
199403	29	233	MUC1-IX	106
199404	30	197	MUC1	3
199404	30	131	MUC1/Y	10
199404	30	164	MUC1-II	11
199404	30	212	MUC1-VI	17
199404	30	233	MUC1-VII	18
199404	30	165	MUC1/X	20
199404	30	176	MUC1/A	100
199404	30	217	MUC1/REP	101
199404	30	1423	MUC1/SEC	102
199404	30	165	MUC1/Z	103
199404	30	356	MUC1-VIII	105
199404	30	234	MUC1-IX	106

199405	31	210	MUC1	3
199405	31	225	MUC1-VI	17
199405	31	246	MUC1-VII	18
199405	31	189	MUC1/A	100
199405	31	230	MUC1/REP	101
199405	31	1436	MUC1/SEC	102
199405	31	369	MUC1-VIII	105
199406	32	214	MUC1	3
199406	32	229	MUC1-VI	17
199406	32	250	MUC1-VII	18
199406	32	193	MUC1/A	100
199406	32	234	MUC1/REP	101
199406	32	1440	MUC1/SEC	102
199406	32	373	MUC1-VIII	105
199407	33	227	MUC1	3
199407	33	242	MUC1-VI	17
199407	33	263	MUC1-VII	18
199407	33	206	MUC1/A	100
199407	33	247	MUC1/REP	101
199407	33	1453	MUC1/SEC	102
199407	33	386	MUC1-VIII	105
199408	34	344	MUC1	3
199408	34	359	MUC1-VI	17
199408	34	380	MUC1-VII	18
199408	34	364	MUC1/REP	101
199408	34	1570	MUC1/SEC	102
199409	35	694	MUC1	3
199409	35	93	MUC1-V	16
199409	35	589	MUC1-VI	17
199409	35	1800	MUC1/SEC	102
199410	36	697	MUC1	3
199410	36	96	MUC1-V	16
199410	36	592	MUC1-VI	17
199410	36	1803	MUC1/SEC	102
199411	37	704	MUC1	3
199411	37	103	MUC1-V	16
199411	37	599	MUC1-VI	17
199411	37	1810	MUC1/SEC	102
199412	38	829	MUC1	3
199412	38	228	MUC1-V	16
199412	38	724	MUC1-VI	17
199412	38	1935	MUC1/SEC	102
199413	39	835	MUC1	3
199413	39	234	MUC1-V	16
199413	39	730	MUC1-VI	17
199413	39	1941	MUC1/SEC	102
199414	40	860	MUC1	3
199414	40	259	MUC1-V	16
199414	40	755	MUC1-VI	17
199414	40	1966	MUC1/SEC	102
199415	41	940	MUC1	3
199415	41	44	MUC1-IV	14
199415	41	339	MUC1-V	16

199415	41	835	MUC1-VI	17
199415	41	2046	MUC1/SEC	102
199416	42	997	MUC1	3
199416	42	151	MUC1/Y	10
199416	42	238	MUC1-II	11
199416	42	101	MUC1-IV	14
199416	42	396	MUC1-V	16
199416	42	892	MUC1-VI	17
199416	42	2103	MUC1/SEC	102
199416	42	239	MUC1/Z	103
199416	42	254	MUC1-IX	106
199417	43	1037	MUC1	3
199417	43	191	MUC1/Y	10
199417	43	278	MUC1-II	11
199417	43	141	MUC1-IV	14
199417	43	436	MUC1-V	16
199417	43	932	MUC1-VI	17
199417	43	206	MUC1/X	20
199417	43	2143	MUC1/SEC	102
199417	43	279	MUC1/Z	103
199417	43	294	MUC1-IX	106
199418	44	1042	MUC1	3
199418	44	196	MUC1/Y	10
199418	44	283	MUC1-II	11
199418	44	146	MUC1-IV	14
199418	44	441	MUC1-V	16
199418	44	937	MUC1-VI	17
199418	44	211	MUC1/X	20
199418	44	2148	MUC1/SEC	102
199418	44	284	MUC1/Z	103
199418	44	299	MUC1-IX	106
199419	45	1056	MUC1	3
199419	45	210	MUC1/Y	10
199419	45	951	MUC1-VI	17
199419	45	298	MUC1/Z	103
199419	45	313	MUC1-IX	106
199420	46	1065	MUC1	3
199420	46	219	MUC1/Y	10
199420	46	3	MUC1-III	12
199420	46	960	MUC1-VI	17
199420	46	2270	MUC1/SEC	102
199420	46	307	MUC1/Z	103
199420	46	322	MUC1-IX	106
199421	47	1091	MUC1	3
199421	47	245	MUC1/Y	10
199421	47	29	MUC1-III	12
199421	47	986	MUC1-VI	17
199421	47	2296	MUC1/SEC	102
199421	47	333	MUC1/Z	103
199421	47	348	MUC1-IX	106
199422	48	1095	MUC1	3
199422	48	249	MUC1/Y	10
199422	48	33	MUC1-III	12

199422	48	990	MUC1-VI	17
199422	48	2300	MUC1/SEC	102
199422	48	337	MUC1/Z	103
199422	48	352	MUC1-IX	106
199423	49	1100	MUC1	3
199423	49	254	MUC1/Y	10
199423	49	38	MUC1-III	12
199423	49	995	MUC1-VI	17
199423	49	2305	MUC1/SEC	102
199423	49	342	MUC1/Z	103
199423	49	357	MUC1-IX	106
199424	50	1112	MUC1	3
199424	50	266	MUC1/Y	10
199424	50	1007	MUC1-VI	17
199424	50	354	MUC1/Z	103
199424	50	369	MUC1-IX	106
199425	51	1115	MUC1	3
199425	51	269	MUC1/Y	10
199425	51	1010	MUC1-VI	17
199425	51	357	MUC1/Z	103
199425	51	372	MUC1-IX	106
199426	52	1168	MUC1	3
199426	52	1063	MUC1-VI	17
199426	52	281	MUC1/X	20
199426	52	2524	MUC1/SEC	102
199426	52	410	MUC1/Z	103
199426	52	425	MUC1-IX	106
199427	53	1217	MUC1	3
199427	53	371	MUC1/Y	10
199427	53	1112	MUC1-VI	17
199427	53	330	MUC1/X	20
199427	53	2573	MUC1/SEC	102
199427	53	459	MUC1/Z	103
199427	53	473	MUC1-IX	106
199428	54	1225	MUC1	3
199428	54	379	MUC1/Y	10
199428	54	1120	MUC1-VI	17
199428	54	338	MUC1/X	20
199428	54	2581	MUC1/SEC	102
199428	54	467	MUC1/Z	103
199428	54	481	MUC1-IX	106
199429	55	1251	MUC1	3
199429	55	405	MUC1/Y	10
199429	55	1146	MUC1-VI	17
199429	55	364	MUC1/X	20
199429	55	493	MUC1/Z	103
199429	55	507	MUC1-IX	106
199430	56	1268	MUC1	3
199430	56	422	MUC1/Y	10
199430	56	69	MUC1-III	12
199430	56	474	MUC1-V	16
199430	56	1163	MUC1-VI	17
199430	56	381	MUC1/X	20

199430	56	510	MUC1/Z	103
199431	57	1371	MUC1	3
199431	57	525	MUC1/Y	10
199431	57	250	MUC1-IV	14
199431	57	577	MUC1-V	16
199431	57	1266	MUC1-VI	17
199431	57	484	MUC1/X	20
199431	57	613	MUC1/Z	103
199431	57	76	MUC1-X	107
199432	58	1397	MUC1	3
199432	58	551	MUC1/Y	10
199432	58	276	MUC1-IV	14
199432	58	603	MUC1-V	16
199432	58	1292	MUC1-VI	17
199432	58	510	MUC1/X	20
199432	58	2977	MUC1/SEC	102
199432	58	639	MUC1/Z	103
199432	58	102	MUC1-X	107
199433	59	1412	MUC1	3
199433	59	566	MUC1/Y	10
199433	59	291	MUC1-IV	14
199433	59	618	MUC1-V	16
199433	59	1307	MUC1-VI	17
199433	59	525	MUC1/X	20
199433	59	2992	MUC1/SEC	102
199433	59	654	MUC1/Z	103
199433	59	117	MUC1-X	107
199434	60	1499	MUC1	3
199434	60	653	MUC1/Y	10
199434	60	425	MUC1-II	11
199434	60	378	MUC1-IV	14
199434	60	704	MUC1-V	16
199434	60	1394	MUC1-VI	17
199434	60	612	MUC1/X	20
199434	60	3078	MUC1/SEC	102
199434	60	741	MUC1/Z	103
199434	60	204	MUC1-X	107
199435	61	1540	MUC1	3
199435	61	694	MUC1/Y	10
199435	61	466	MUC1-II	11
199435	61	419	MUC1-IV	14
199435	61	1435	MUC1-VI	17
199435	61	653	MUC1/X	20
199435	61	782	MUC1/Z	103
199436	62	1582	MUC1	3
199436	62	736	MUC1/Y	10
199436	62	508	MUC1-II	11
199436	62	786	MUC1-V	16
199436	62	1477	MUC1-VI	17
199436	62	695	MUC1/X	20
199436	62	824	MUC1/Z	103
199437	63	1586	MUC1	3
199437	63	740	MUC1/Y	10

199437	63	512	MUC1-II	11
199437	63	790	MUC1-V	16
199437	63	1481	MUC1-VI	17
199437	63	699	MUC1/X	20
199437	63	828	MUC1/Z	103
199438	64	1594	MUC1	3
199438	64	520	MUC1-II	11
199438	64	798	MUC1-V	16
199438	64	1489	MUC1-VI	17
199438	64	707	MUC1/X	20
199438	64	836	MUC1/Z	103
199439	65	1606	MUC1	3
199440	66	1617	MUC1	3
199441	67	1622	MUC1	3
199441	67	1517	MUC1-VI	17
199442	68	1630	MUC1	3
199442	68	833	MUC1-V	16
199442	68	1525	MUC1-VI	17
199443	69	1635	MUC1	3
199443	69	514	MUC1-IV	14
199443	69	1530	MUC1-VI	17
199444	70	141	MUC1/Y	10
199444	70	244	MUC1-IX	106
199445	71	174	MUC1-II	11
199445	71	175	MUC1/Z	103
199446	72	297	MUC1-II	11
199447	73	49	MUC1-III	12
199448	74	3171	MUC1/SEC	102
199448	74	298	MUC1-X	107
199449	75	3279	MUC1/SEC	102
199449	75	407	MUC1-X	107
199450	76	559	MUC1-X	107
199451	77	160	MUC1-IV	14
199452	78	1134	MUC1/SEC	102
199452	78	65	MUC1-VIII	105
199453	79	1269	MUC1/SEC	102
199453	79	202	MUC1-VIII	105
199454	80	455	MUC1-V	16
199455	81	1776	MUC1-VI	17
199456	82	115	MUC1-VII	18
199456	82	58	MUC1/A	100
199456	82	99	MUC1/REP	101
199456	82	116	MUC1-IX	106
199457	83	175	MUC1/X	20
199458	84	1132	MUC1	3
199458	84	286	MUC1/Y	10
199458	84	1027	MUC1-VI	17
199458	84	245	MUC1/X	20
199458	84	2488	MUC1/SEC	102
199458	84	374	MUC1/Z	103
199458	84	389	MUC1-IX	106
199459	85	122	MUC1/D	21
199460	86	85	MUC1/A	100

199460	86	126	MUC1/REP	101
199460	86	1332	MUC1/SEC	102
199461	87	115	MUC1	3
199461	87	82	MUC1-II	11
199461	87	130	MUC1-VI	17
199461	87	83	MUC1/X	20
199461	87	94	MUC1/A	100
199461	87	135	MUC1/REP	101
199461	87	1341	MUC1/SEC	102
199461	87	83	MUC1/Z	103
199462	88	147	MUC1	3
199462	88	81	MUC1/Y	10
199462	88	114	MUC1-II	11
199462	88	162	MUC1-VI	17
199462	88	183	MUC1-VII	18
199462	88	115	MUC1/X	20
199462	88	126	MUC1/A	100
199462	88	167	MUC1/REP	101
199462	88	1373	MUC1/SEC	102
199462	88	115	MUC1/Z	103
199462	88	154	MUC1/C	104
199462	88	306	MUC1-VIII	105
199462	88	184	MUC1-IX	106
199463	89	188	MUC1	3
199463	89	122	MUC1/Y	10
199463	89	155	MUC1-II	11
199463	89	203	MUC1-VI	17
199463	89	224	MUC1-VII	18
199463	89	156	MUC1/X	20
199463	89	167	MUC1/A	100
199463	89	208	MUC1/REP	101
199463	89	1414	MUC1/SEC	102
199463	89	156	MUC1/Z	103
199463	89	347	MUC1-VIII	105
199463	89	225	MUC1-IX	106
199464	90	207	MUC1	3
199464	90	222	MUC1-VI	17
199464	90	243	MUC1-VII	18
199464	90	186	MUC1/A	100
199464	90	227	MUC1/REP	101
199464	90	1433	MUC1/SEC	102
199464	90	366	MUC1-VIII	105
199465	91	710	MUC1	3
199465	91	109	MUC1-V	16
199465	91	605	MUC1-VI	17
199465	91	1816	MUC1/SEC	102
199466	92	938	MUC1	3
199466	92	42	MUC1-IV	14
199466	92	337	MUC1-V	16
199466	92	833	MUC1-VI	17
199466	92	2044	MUC1/SEC	102
199467	93	987	MUC1	3
199467	93	228	MUC1-II	11

199467	93	91	MUC1-IV	14
199467	93	386	MUC1-V	16
199467	93	882	MUC1-VI	17
199467	93	2093	MUC1/SEC	102
199467	93	229	MUC1/Z	103
199468	94	1006	MUC1	3
199468	94	160	MUC1/Y	10
199468	94	247	MUC1-II	11
199468	94	110	MUC1-IV	14
199468	94	405	MUC1-V	16
199468	94	901	MUC1-VI	17
199468	94	2112	MUC1/SEC	102
199468	94	248	MUC1/Z	103
199468	94	263	MUC1-IX	106
199469	95	2466	MUC1/SEC	102
199470	96	1281	MUC1	3
199470	96	435	MUC1/Y	10
199470	96	82	MUC1-III	12
199470	96	487	MUC1-V	16
199470	96	1176	MUC1-VI	17
199470	96	394	MUC1/X	20
199470	96	523	MUC1/Z	103
199470	96	538	MUC1-IX	106
199471	97	3292	MUC1/SEC	102
199471	97	420	MUC1-X	107

What is claimed is:

1. A compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding mucin 1, transmembrane, wherein said compound specifically hybridizes with said nucleic acid molecule encoding mucin 1, transmembrane and inhibits the expression of mucin 1, transmembrane.

2. The compound of claim 1 which is an antisense oligonucleotide.

3. The compound of claim 2 wherein the antisense oligonucleotide has a sequence comprising SEQ ID NO: 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 42, 43, 44, 45, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 64, 66, 67, 68, 69, 72, 74, 75, 76, 78, 79, 80, 81, 88, 89, 90, 91, 93, 94, 96, 97, 98 or 99.

4. The compound of claim 2 wherein the antisense oligonucleotide comprises at least one modified internucleoside linkage.

5. The compound of claim 4 wherein the modified internucleoside linkage is a phosphorothioate linkage.

6. The compound of claim 2 wherein the antisense oligonucleotide comprises at least one modified sugar moiety.

7. The compound of claim 6 wherein the modified sugar moiety is a 2'-O-methoxyethyl sugar moiety.

8. The compound of claim 2 wherein the antisense oligonucleotide comprises at least one modified nucleobase.

9. The compound of claim 8 wherein the modified nucleobase is a 5-methylcytosine.

10. The compound of claim 2 wherein the antisense oligonucleotide is a chimeric oligonucleotide.

11. A compound 8 to 50 nucleobases in length which specifically hybridizes with at least an 8-nucleobase portion of an active site on a nucleic acid molecule encoding mucin 1, transmembrane.

12. A composition comprising the compound of claim 1 and a pharmaceutically acceptable carrier or diluent.

13. The composition of claim 12 further comprising a colloidal dispersion system.

14. The composition of claim 12 wherein the compound is an antisense oligonucleotide.

15. A method of inhibiting the expression of mucin 1, transmembrane in cells or tissues comprising contacting said cells or tissues with the compound of claim 1 so that expression of mucin 1, transmembrane is inhibited.

16. A method of treating an animal having a disease or condition associated with mucin 1, transmembrane comprising administering to said animal a therapeutically or prophylactically effective amount of the compound of claim 1 so that expression of mucin 1, transmembrane is inhibited.

17. The method of claim 16 wherein the disease or condition is a hyperproliferative disorder.

18. The method of claim 16 wherein the disease or disorder is an inflammatory disorder.

19. The compound of claim 1 targeted to a nucleic acid molecule encoding mucin 1, transmembrane, wherein said compound specifically hybridizes with and differentially inhibits the expression of one of the variants of mucin 1, transmembrane relative to the remaining variants of of mucin 1, transmembrane.

20. The compound of claim 19 targeted to a nucleic acid molecule encoding of mucin 1, transmembrane, wherein said compound hybridizes with and specifically inhibits the expression of a variant of of mucin 1, transmembrane, wherein said variant is selected from the group consisting of MUC1, MUC1/Y, MUC1/X, MUC1/D, MUC1/A, MUC1/REP, MUC1/SEC, MUC1/Z, MUC1/C, MUC1-II, MUC1-III, MUC1-IV, MUC1-V, MUC1-VI, MUC1-VII, MUC1-VIII, MUC1-IX and MUC1-X.

SEQUENCE LISTING

<110> Kenneth W. Dobie
Susan J. Myers
Isis Pharmaceuticals, Inc.

<120> ANTISENSE MODULATION OF MUCIN 1, TRANSMEMBRANE EXPRESSION

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<151> 2001-12-20

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gga gaa aag gag act tcg gct acc cag aga agt tca gtg ccc agc tct      201
Gly Glu Lys Glu Thr Ser Ala Thr Gln Arg Ser Ser Val Pro Ser Ser
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act gag aag aat gct gtg agt atg acc agc agc gta ctc tcc agc cac      249
Thr Glu Lys Asn Ala Val Ser Met Thr Ser Ser Val Leu Ser Ser His
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agc ccc ggt tca ggc tcc tcc acc act cag gga cag gat gtc act ctg      297
Ser Pro Gly Ser Gly Ser Ser Thr Thr Gln Gly Gln Asp Val Thr Leu
65                  70                  75                  80

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Ala Pro Ala Thr Glu Pro Ala Ser Gly Ser Ala Ala Thr Trp Gly Gln
                85                  90                  95

gat gtc acc tcg gtc cca gtc acc agg cca gcc ctg ggc tcc acc acc      393
Asp Val Thr Ser Val Pro Val Thr Arg Pro Ala Leu Gly Ser Thr Thr
            100                 105                 110

ccg cca gcc cac gat gtc acc tca gcc ccg gac aac aag cca gcc ccg      441
Pro Pro Ala His Asp Val Thr Ser Ala Pro Asp Asn Lys Pro Ala Pro
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ggc tcc acc gcc ccc cca gcc cac ggt gtc acc tcg gcc ccg gac acc      489
Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr
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agg ccg ccc ccg ggc tcc acc gcc ccc cca gcc cac ggt gtc acc tcg      537
Arg Pro Pro Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser
145                 150                 155                 160

gcc ccg gac acc agg ccg ccc ccg ggc tcc acc gcg ccc gca gcc cac      585
Ala Pro Asp Thr Arg Pro Pro Pro Gly Ser Thr Ala Pro Ala Ala His
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ggt gtc acc tcg gcc ccg gac acc agg ccg gcc ccg ggc tcc acc gcc      633
Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala
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ccc cca gcc cat ggt gtc acc tcg gcc ccg gac aac agg ccc gcc ttg      681
Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Asn Arg Pro Ala Leu
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Ala Ser Gly Ser Ala Ser Thr Leu Val His Asn Gly Thr Ser Ala Arg
225                 230                 235                 240
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Ala Thr Thr Thr Pro Ala Ser Lys Ser Thr Pro Phe Ser Ile Pro Ser
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cac cac tct gat act cct acc acc ctt gcc agc cat agc acc aag act      873
His His Ser Asp Thr Pro Thr Thr Leu Ala Ser His Ser Thr Lys Thr
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gat gcc agt agc act cac cat agc acg gta cct cct ctc acc tcc tcc      921
Asp Ala Ser Ser Thr His His Ser Thr Val Pro Pro Leu Thr Ser Ser
        275                 280                 285

aat cac agc act tct ccc cag ttg tct act ggg gtc tct ttc ttt ttc      969
Asn His Ser Thr Ser Pro Gln Leu Ser Thr Gly Val Ser Phe Phe Phe
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ctg tct ttt cac att tca aac ctc cag ttt aat tcc tct ctg gaa gat     1017
Leu Ser Phe His Ile Ser Asn Leu Gln Phe Asn Ser Ser Leu Glu Asp
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ccc agc acc gac tac tac caa gag ctg cag aga gac att tct gaa atg     1065
Pro Ser Thr Asp Tyr Tyr Gln Glu Leu Gln Arg Asp Ile Ser Glu Met
                325                 330                 335

ttt ttg cag att tat aaa caa ggg ggt ttt ctg ggc ctc tcc aat att     1113
Phe Leu Gln Ile Tyr Lys Gln Gly Gly Phe Leu Gly Leu Ser Asn Ile
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aag ttc agg cca gga tct gtg gtg gta caa ttg act ctg gcc ttc cga     1161
Lys Phe Arg Pro Gly Ser Val Val Val Gln Leu Thr Leu Ala Phe Arg
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gaa ggt acc atc aat gtc cac gac gtg gag aca cag ttc aat cag tat     1209
Glu Gly Thr Ile Asn Val His Asp Val Glu Thr Gln Phe Asn Gln Tyr
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aaa acg gaa gca gcc tct cga tat aac ctg acg atc tca gac gtc agc     1257
Lys Thr Glu Ala Ala Ser Arg Tyr Asn Leu Thr Ile Ser Asp Val Ser
385                 390                 395                 400

gtg agt gat gtg cca ttt cct ttc tct gcc cag tct ggg gct ggg gtg     1305
Val Ser Asp Val Pro Phe Pro Phe Ser Ala Gln Ser Gly Ala Gly Val
                405                 410                 415

cca ggc tgg ggc atc gcg ctg ctg gtg ctg gtc tgt gtt ctg gtt gcg     1353
Pro Gly Trp Gly Ile Ala Leu Leu Val Leu Val Cys Val Leu Val Ala
            420                 425                 430

ctg gcc att gtc tat ctc att gcc ttg gct gtc tgt cag tgc cgc cga     1401
Leu Ala Ile Val Tyr Leu Ile Ala Leu Ala Val Cys Gln Cys Arg Arg
        435                 440                 445

aag aac tac ggg cag ctg gac atc ttt cca gcc cgg gat acc tac cat     1449
Lys Asn Tyr Gly Gln Leu Asp Ile Phe Pro Ala Arg Asp Thr Tyr His
    450                 455                 460

cct atg agc gag tac ccc acc tac cac acc cat ggg cgc tat gtg ccc     1497
Pro Met Ser Glu Tyr Pro Thr Tyr His Thr His Gly Arg Tyr Val Pro
465                 470                 475                 480
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Pro Ser Ser Thr Asp Arg Ser Pro Tyr Glu Lys Val Ser Ala Gly Asn
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Gly Gly Ser Ser Leu Ser Tyr Thr Asn Pro Ala Val Ala Ala Thr Ser
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gcc aac ttg tag gggcacgtcg ccctctgagc tgagtggcca gccagtgcca 1645
Ala Asn Leu
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1 5 10 15

gtg ctt aca ggt tct ggt cat gca agc tct acc cca ggt gga gaa aag 96
Val Leu Thr Gly Ser Gly His Ala Ser Ser Thr Pro Gly Gly Glu Lys
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Glu Thr Ser Ala Thr Gln Arg Ser Ser Val Pro Ser Ser Thr Glu Lys
35 40 45

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aat gct ttt aat tcc tct ctg gaa gat ccc agc acc gac tac tac caa      192
Asn Ala Phe Asn Ser Ser Leu Glu Asp Pro Ser Thr Asp Tyr Tyr Gln
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gag ctg cag aga gac att tct gaa atg ttt ttg cag att tat aaa caa      240
Glu Leu Gln Arg Asp Ile Ser Glu Met Phe Leu Gln Ile Tyr Lys Gln
 65                  70                  75                  80

ggg ggt ttt ctg ggc ctc tcc aat att aag ttc agg cca gga tct gtg      288
Gly Gly Phe Leu Gly Leu Ser Asn Ile Lys Phe Arg Pro Gly Ser Val
                 85                  90                  95

gtg gta caa ttg act ctg gcc ttc cga gaa ggt acc atc aat gtc cac      336
Val Val Gln Leu Thr Leu Ala Phe Arg Glu Gly Thr Ile Asn Val His
            100                 105                 110

gac atg gag aca cag ttc aat cag tat aaa acg gaa gca gcc tct cga      384
Asp Met Glu Thr Gln Phe Asn Gln Tyr Lys Thr Glu Ala Ala Ser Arg
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tat aac ctg acg atc tca gac gtc agc gtg agt gat gtg cca ttt cct      432
Tyr Asn Leu Thr Ile Ser Asp Val Ser Val Ser Asp Val Pro Phe Pro
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ttc tct gcc cag tct ggg gct ggg gtg cca ggc tgg ggc atc gcg ctg      480
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ctg gtg ctg gtc tgt gtt ctg gtt gcg ctg gcc att gtc tat ctc att      528
Leu Val Leu Val Cys Val Leu Val Ala Leu Ala Ile Val Tyr Leu Ile
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gcc ttg gct gtc tgt cag tgc cgc cga aag aac tac ggg cag ctg gac      576
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Ile Phe Pro Ala Arg Asp Thr Tyr His Pro Met Ser Glu Tyr Pro Thr
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Tyr His Thr His Gly Arg Tyr Val Pro Pro Ser Ser Thr Asp Arg Ser
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Pro Tyr Glu Lys Val Ser Ala Gly Asn Gly Gly Ser Ser Leu Ser Tyr
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cat gca agc tct acc cca ggt gga gaa aag gag act tcg gct acc cag 147
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aga agt tca gtg ccc agc tct act gag aag aat gct ttg tct act ggg 195
Arg Ser Ser Val Pro Ser Ser Thr Glu Lys Asn Ala Leu Ser Thr Gly
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gtc tct ttc ttt ttc ctg tct ttt cac att tca aac ctc cag ttt aat 243
Val Ser Phe Phe Phe Leu Ser Phe His Ile Ser Asn Leu Gln Phe Asn
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tcc tct ctg gaa gat ccc agc acc gac tac tac caa gag ctg cag aga 291
Ser Ser Leu Glu Asp Pro Ser Thr Asp Tyr Tyr Gln Glu Leu Gln Arg
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gac att tct gaa atg gct gtc tgt cag tgc cgc cga aag aac tac ggg 339
Asp Ile Ser Glu Met Ala Val Cys Gln Cys Arg Arg Lys Asn Tyr Gly
90 95 100 105

ctg ctg gac atc ttt cca gcc cgg gat acc tac cat cct atg agc gag 387
Leu Leu Asp Ile Phe Pro Ala Arg Asp Thr Tyr His Pro Met Ser Glu
110 115 120

tac ccc acc tac cac acc cat ggg cgc tat gtg ccc cct agc agt acc 435
Tyr Pro Thr Tyr His Thr His Gly Arg Tyr Val Pro Pro Ser Ser Thr
125 130 135

gat cgt agc ccc tat gag aag gtt tct gca ggt aat ggt ggc agc agc 483
Asp Arg Ser Pro Tyr Glu Lys Val Ser Ala Gly Asn Gly Gly Ser Ser
140 145 150

ctc tct tac aca aac cca gca gtg gca gcc act tct gcc aac ttg tag 531
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cg 122

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Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu
1 5 10

ctc ctc aca gtg ctt aca gtt gtt aca ggt tct ggt cat gca agc tct 159
Leu Leu Thr Val Leu Thr Val Val Thr Gly Ser Gly His Ala Ser Ser
15 20 25

acc cca ggt gga gaa aag gag act tcg gct acc cag aga agt tca gtg 207
Thr Pro Gly Gly Glu Lys Glu Thr Ser Ala Thr Gln Arg Ser Ser Val
30 35 40 45

ccc agc tct act gag aag aat gct gtg agt atg acc agc agc gta ctc 255
Pro Ser Ser Thr Glu Lys Asn Ala Val Ser Met Thr Ser Ser Val Leu
50 55 60

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Ser Ser His Ser Pro Gly Ser Gly Ser Ser Thr Thr Gln Gly Gln Asp
65 70 75

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        80                  85                  90

tgg gga cag gat gtc acc tcg gtc cca gtc acc agg cca gcc ctg ggc      399
Trp Gly Gln Asp Val Thr Ser Val Pro Val Thr Arg Pro Ala Leu Gly
    95                  100                 105

tcc acc acc ccg cca gcc cac gat gtc acc tca gcc ccg gac aac aag      447
Ser Thr Thr Pro Pro Ala His Asp Val Thr Ser Ala Pro Asp Asn Lys
110                 115                 120                 125

cca gcc ccg ggc tcc acc gcc ccc cca gcc cac ggt gtc acc tcg gcc      495
Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala
                130                 135                 140

ccg gac acc agg ccg gcc ccg ggc tcc acc gcc ccc cca gcc cat ggt      543
Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly
            145                 150                 155

gtc acc tcg gcc ccg gac aac agg ccc gcc ttg ggc tcc acc gcc cct      591
Val Thr Ser Ala Pro Asp Asn Arg Pro Ala Leu Gly Ser Thr Ala Pro
        160                 165                 170

cca gtc cac aat gtc acc tcg gcc tca ggc tct gca tca ggc tca gct      639
Pro Val His Asn Val Thr Ser Ala Ser Gly Ser Ala Ser Gly Ser Ala
    175                 180                 185

tct act ctg gtg cac aac ggc acc tct gcc agg gct acc aca acc cca      687
Ser Thr Leu Val His Asn Gly Thr Ser Ala Arg Ala Thr Thr Thr Pro
190                 195                 200                 205

gcc agc aag agc act cca ttc tca att ccc agc cac cac tct gat act      735
Ala Ser Lys Ser Thr Pro Phe Ser Ile Pro Ser His His Ser Asp Thr
                210                 215                 220

cct acc acc ctt gcc agc cat agc acc aag act gat gcc agt agc act      783
Pro Thr Thr Leu Ala Ser His Ser Thr Lys Thr Asp Ala Ser Ser Thr
            225                 230                 235

cac cat agc acg gta cct cct ctc acc tcc tcc aat cac agc act tct      831
His His Ser Thr Val Pro Pro Leu Thr Ser Ser Asn His Ser Thr Ser
        240                 245                 250

ccc cag ttg tct act ggg gtc tct ttc ttt ttc ctg tct ttt cac att      879
Pro Gln Leu Ser Thr Gly Val Ser Phe Phe Phe Leu Ser Phe His Ile
    255                 260                 265

tca aac ctc cag ttt aat tcc tct ctg gaa gat ccc agc acc gac tac      927
Ser Asn Leu Gln Phe Asn Ser Ser Leu Glu Asp Pro Ser Thr Asp Tyr
270                 275                 280                 285

tac caa gag ctg cag aga gac att tct gaa atg ttt ttg cag att tat      975
Tyr Gln Glu Leu Gln Arg Asp Ile Ser Glu Met Phe Leu Gln Ile Tyr
                290                 295                 300

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Lys Gln Gly Gly Phe Leu Gly Leu Ser Asn Ile Lys Phe Arg Pro Gly
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Ser Val Val Val Gln Leu Thr Leu Ala Phe Arg Glu Gly Thr Ile Asn
        320                 325                 330

gtc cac gac gtg gag aca cag ttc aat cag tat aaa acg gaa gca gcc    1119
Val His Asp Val Glu Thr Gln Phe Asn Gln Tyr Lys Thr Glu Ala Ala
    335                 340                 345

tct cga tat aac ctg acg atc tca gac gtc agc gtg agt gat gtg cca    1167
Ser Arg Tyr Asn Leu Thr Ile Ser Asp Val Ser Val Ser Asp Val Pro
350                 355                 360                 365

ttt cct ttc tct gcc cag tct ggg gct ggg gtg cca ggc tgg ggc atc    1215
Phe Pro Phe Ser Ala Gln Ser Gly Ala Gly Val Pro Gly Trp Gly Ile
                370                 375                 380

gcg ctg ctg gtg ctg gtc tgt gtt ctg gtt gcg ctg gcc att gtc tat    1263
Ala Leu Leu Val Leu Val Cys Val Leu Val Ala Leu Ala Ile Val Tyr
            385                 390                 395

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Leu Ile Ala Leu Ala Val Cys Gln Cys Arg Arg Lys Asn Tyr Gly Gln
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ctg gac atc ttt cca gcc cgg gat acc tac cat cct atg agc gag tac    1359
Leu Asp Ile Phe Pro Ala Arg Asp Thr Tyr His Pro Met Ser Glu Tyr
    415                 420                 425

ccc acc tac cac acc cat ggg cgc tat gtg ccc cct agc agt acc gat    1407
Pro Thr Tyr His Thr His Gly Arg Tyr Val Pro Pro Ser Ser Thr Asp
430                 435                 440                 445

cgt agc ccc tat gag aag gtt tct gca ggt aat ggt ggc agc agc ctc    1455
Arg Ser Pro Tyr Glu Lys Val Ser Ala Gly Asn Gly Gly Ser Ser Leu
                450                 455                 460

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Ser Tyr Thr Asn Pro Ala Val Ala Ala Thr Ser Ala Asn Leu
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Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu
1 5 10

ctc aca gtg ctt aca gct acc aca gcc cct aaa ccc gca aca gtt gtt 156
Leu Thr Val Leu Thr Ala Thr Thr Ala Pro Lys Pro Ala Thr Val Val
15 20 25 30

acg ggt tct ggt cat gca agc tct acc cca ggt gga gaa aag gag act 204
Thr Gly Ser Gly His Ala Ser Ser Thr Pro Gly Gly Glu Lys Glu Thr
35 40 45

tcg gct acc cag aga agt tca gtg ccc agc tct act gag aag aat gct 252
Ser Ala Thr Gln Arg Ser Ser Val Pro Ser Ser Thr Glu Lys Asn Ala
50 55 60

gtg agt atg acc agc agc gta ctc tcc agc cac agc ccc ggt tca ggc 300
Val Ser Met Thr Ser Ser Val Leu Ser Ser His Ser Pro Gly Ser Gly
65 70 75

tcc tcc acc act cag gga cag gat gtc act ctg gcc ccg gcc acg gaa 348
Ser Ser Thr Thr Gln Gly Gln Asp Val Thr Leu Ala Pro Ala Thr Glu
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Pro Ala Ser Gly Ser Ala Ala Thr Trp Gly Gln Asp Val Thr Ser Val
95 100 105 110

cca gtc acc agg cca gcc ctg ggc tcc acc acc ccg cca gcc cac gat 444
Pro Val Thr Arg Pro Ala Leu Gly Ser Thr Thr Pro Pro Ala His Asp
115 120 125

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Val Thr Ser Ala Pro Asp Asn Lys Pro Ala Pro Gly Ser Thr Ala Pro
130 135 140

caa gcc cac ggt gtc acc tcg gcc ccg gac acc agg ccg gcc ccg ggc 540
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Phe Leu Leu Leu Leu Leu Thr Val Leu Thr Val Val Thr Gly Ser Gly
10 15 20 25

cat gca agc tct acc cca ggt gga gaa aag gag act tcg gct acc cag 148
His Ala Ser Ser Thr Pro Gly Gly Glu Lys Glu Thr Ser Ala Thr Gln
30 35 40

aga agt tca gtg ccc agc tct act gag aag aat gct atc cca gca ccg 196
Arg Ser Ser Val Pro Ser Ser Thr Glu Lys Asn Ala Ile Pro Ala Pro
45 50 55

act act acc aag agc tgc aga gag aca ttt ctg aaa tgg cca gga tct 244
Thr Thr Thr Lys Ser Cys Arg Glu Thr Phe Leu Lys Trp Pro Gly Ser
60 65 70

gtg gtg gta caa ttg act ctg gcc ttc cga gaa ggt acc atc aat gtc 292
Val Val Val Gln Leu Thr Leu Ala Phe Arg Glu Gly Thr Ile Asn Val
75 80 85

cac gac gtg gag aca cag ttc aat cag tat aaa acg gaa gca gcc tct 340
His Asp Val Glu Thr Gln Phe Asn Gln Tyr Lys Thr Glu Ala Ala Ser
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cga tat aac ctg acg atc tca gac gtc agc gtg agt gat gtg cca ttt 388
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Pro Phe Ser Ala Gln Ser Gly Ala Gly Val Pro Gly Trp Gly Ile Ala
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Ile Ala Leu Ala Val Cys Gln Cys Arg Arg Lys Asn Tyr Gly Gln Leu
    155                 160                 165

gac atc ttt cca gcc cgg gat acc tac cat cct atg agc gag tac ccc      580
Asp Ile Phe Pro Ala Arg Asp Thr Tyr His Pro Met Ser Glu Tyr Pro
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Thr Tyr His Thr His Gly Arg Tyr Val Pro Pro Ser Ser Thr Asp Arg
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agc ccc tat gag aag gtt tct gca ggt aat ggt ggc agc agc ctc tct      676
Ser Pro Tyr Glu Lys Val Ser Ala Gly Asn Gly Gly Ser Ser Leu Ser
            205                 210                 215

tac aca aac cca gca gtg gca gcc act tct gcc aac ttg tag gggcacgtcg  728
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                 1               5                  10

ctg ctc ctc aca gtg ctt aca ggt gga gaa aag gag act tcg gct acc      157
Leu Leu Leu Thr Val Leu Thr Gly Gly Glu Lys Glu Thr Ser Ala Thr
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<220>

<221> misc_feature
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